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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/602,812	06/23/2000	Camellia W. Adams	P1467R2	9612

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EXAMINER
HUNT, JENNIFER ELIZABETH

ART UNIT	PAPER NUMBER
1642	10

DATE MAILED: 04/01/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/602,812	ADAMS ET AL.	
	Examiner	Art Unit	
	Jennifer E Hunt	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-59* is/are pending in the application.

4a) Of the above claim(s) *9-11,14,15,22,23 and 30-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,12,13,16-21 and 24-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 1-9, 12-13, 16-22, 24-29, and 34 in Paper No. 8, and further election without traverse of the species (B) antibody is not conjugated to a cytotoxic agent and species (D) lung cancer is acknowledged.

2. Claims 1-59 are pending in the application. Claims 10-11, 14-15, 23, 30-33, and 35-59 have been withdrawn from consideration as being drawn to a non-elected Group of invention. Claims 9, 22, 28-29, and 34 are withdrawn from consideration as being drawn to a non-elected species of invention. Claims 1-8, 12-13, 16-21, and 24-27, are addressed herein.

Specification

3. The use of the trademark HERCEPTIN ® has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Information Disclosure Statement

4. The Information Disclosure Statement (PTO-1449) filed 09-01-2000 is acknowledged; however, copies of the references cited therein are not in the instant case. The examiner is making efforts to locate these references; however, resubmission of these documents, if possible, by applicant would facilitate their consideration and would be greatly appreciated by the examiner.

5. Further, the Information Disclosure Statement (PTO-1449) filed 01-29-2001 is acknowledged; however, the 1449 form and copies of the references cited therein are not in the instant case.

6. Further, the Information Disclosure Statement (PTO-1449) filed 10-30-2001 is acknowledged; however, the 1449 form and copies of the references cited therein are not in the instant case.

7. A signed copy of the pertinent PTO-1449's will be mailed as soon as the examiner obtains copies of the forms and references.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-8, 12-13, 16-21, and 24-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating an breast, lung, or prostate cancer in xenograft models, wherein the cancer overexpresses ErbB2, using the anti- ErbB2 antibody 2C4, 7C2, or 4D5, does not

reasonably provide enablement for treating any human having any cancer which expresses EGFR using any antibody which binds ErbB2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented in the specification, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability of the unpredictability of the art, and 8) the breadth of the claims (see Ex parte Forman, 230 USPQ 546, BPAI, 1986).

Claim 1 is broadly drawn to a method of treating an EGFR expressing cancer in a human by administering an antibody which binds ErbB2. Dependent claim 2 further recites that the antibody blocks ligand activation of an ErbB receptor. Dependent claims 3, 16 and 17 respectively recite that the antibody blocks binding of 2C4, has the biological characteristics of 2C4, and is 2C4. Dependent claims 4-6 respectively recite that the cancer is characterized by overexpression of EGFR, that the cancer overexpresses an ErbB ligand, and that the ligand is TGF-alpha. Dependent claim 7 recites that the antibody blocks TGF-alpha activation of mitogen activated protein kinase (MAPK). Dependent claim 8 recites that the cancer is not characterized by overexpression of the ErbB2 receptor. Dependent claims 12 and 13 recite that the cancer is lung cancer, and non-small cell lung cancer, respectively. Dependent claims 18 and 19 respectively recite that the antibody is an antibody fragment, and that the

fragment is an Fab fragment. Dependent claims 20 and 21 recite that the antibody, and the antibody fragment is not conjugated to a cytotoxic agent. Dependent, claims 24-26 specify dosages. Claim 27 is broadly drawn to a method of treating cancer in a human by administering an antibody which binds ErbB2, provided that the cancer is not characterized by overexpression of the ErbB2 receptor.

The specification teaches that 2C4 but not HERCEPTIN ® (which is a humanized 4D5 antibody) is able to block TGF-alpha, HRG or EGF activation of MPAK and p13. The specification further teaches that administration of the monoclonal antibodies 2C4, 7C2, and HERCERPTIN ® each inhibits growth in a lung cancer xenograft model. Additionally, the specification teaches that the monoclonal antibody 2C4 "inhibits growth of xenograft models in vivo" (in references to colon cancer xenografts), but no data is provided. Also, the specification provides an in vitro assay in which MDA-175 cells (which express low levels of ErbB2) are growth inhibited to a greater extent by 2C4 than by HERCEPTIN ®. In this example, however, the extent of the inhibition is not clear since no control was provided for the assay. Lastly, the specification discloses that when MCF7 xenograft mice are administered 2C4, they demonstrate a reduction in growth compared to a control, although tumor growth still occurs.

Thus the claims are broadly drawn, the guidance and the examples provided in the specification are narrow, and the state of the art and the nature of the invention is unpredictable and complex.

With regard to the broadly claimed "antibody which binds ErbB2," the specification has not demonstrated the reproducible production of antibodies which

have properties identical to 2C4 or HERCEPTIN ® nor of antibodies of other species origin which have the claimed properties. The production of a hybridoma which secretes a monoclonal antibody having a particular set of specifically defined characteristics is an unpredictable event. The specification fails to set forth the reproducibility of the generically claimed method of treatment using an antibody which binds ErbB2 and blocks any ErbB receptor, and further which blocks TGF-alpha activation of MAPK. In view of the unpredictability of producing antibodies having the claimed properties from among the 10^6- 10^{10} possible antibody variable region specificities encoded in the mammalian genome and in view of the lack of disclosure of the reproducibility of these antibodies, it does not appear that the antibodies required for the broadly claimed methods can be reproduced from the written disclosure alone. Further it is established in the art that antibodies to the ErbB2 receptor exhibit highly variant activity. For example, Xu et al., Int. J. Cancer, Vol. 53, pages 401-408, 1993 (IDS #110) described a panel of 10 anti-HER2 Mab's which exhibit distinct binding characteristics and activities, including antibodies which do not induce a cytotoxic or cytostatic effect (see abstract). Also, Shepard et al., Journal of Clinical Immunology, Vol. 11, No. 3, 1991, pages 117-126 (IDS #93) describes a panel of 9 anti-HER2 Mab's which exhibit distinct binding characteristics and activities, including antibodies which do not induce a cytotoxic or cytostatic effect (see pages 119-120.)

With regard to claims which are drawn to treating a human having any cancer which expresses EGFR, the claims recite methods which encompass the experimental

and unpredictable field of in vivo therapy for cancer in humans. Articles by Dillman et al. (*J Clin Onco Vol 12, No 7, pages 1497-1515, 07/1997)* and *Dermer (BIO/TECHNOLOGY, Vol 12, page 320, 03/1994*) are cited in order to establish the general state of the art and the level of predictability of in vivo therapy . Dillman et al, while discussing observations related to antibody therapy, teach that "on the negative side is the observation that clinical results do not necessarily improve when humanized chimeric antibodies are used in humans, to spite encouraging in vitro results in CDC or ADDC" (page 1506, col 2 paragraph 3). Dermer teaches that "What is significant in culture, for example immunotherapy's killing power or the transformation of 3T3 cells by a mutated proto-oncogene, simply does not have the same significance for cells in vivo."

Those of skill in the art recognize that in vitro assays are generally useful to screen the effects of agents on target cells. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo experiment as compared to the very narrowly defined and controlled conditions of an in vitro assay does not permit a single extrapolation of in vitro assays to mammal or human therapeutics with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Further even in vivo model results fail to accurately correlate with corresponding results in human patients, due the significantly more complex systems of humans compared to genetically modified and simplified models.

A therapeutic agent must accomplish several tasks to be effective: it must be delivered into circulation and interact at the proper site of action, and it must do so at a therapeutic concentration and remain effective for a sufficient period of time. In vitro assays and animal models cannot duplicate the complex conditions of in vivo therapy of humans. In assays, the agent is in contact with the cells during the entire exposure period, whereas in the case of in vivo therapy, exposure at the target site may be delayed or insufficient.

Further, the claims do not recite that the cancer which is being treated need express ErbB2 at all. While it is reasonable to determine that administration of an anti- ErbB2 antibody might inhibit EGFR/ ErbB2 interactions, which are known in the art to interact with each other in a common tyrosine kinase activation pathway, it is not clear how this might work if a cell does not express ErbB2. There is no guidance or objective evidence that an antibody which binds ErbB2 would have any effect at all on a cell which does not express the ErbB2 receptor, nor is there any guidance or objective evidence that the antibody would be capable of producing a therapeutic effect in humans who have any EGFR overexpressing cancer. Although Example 7 of the instant application sets forth an in vitro assay in which a cell line which expresses but does not "overexpress" ErbB2 exhibits a reduction in tumor growth after administration of 2C4, there is no control antibody or cell line in this sample, and so the specific effect of the anti-ErbB2 antibody 2C4 cannot be determined. Further, the example tests a single cell line, in vitro, which is administered a single species of ErbB2 antibody and thus it is not clear that results obtained from this assay would

correlate to generalized results of administering an anti ErbB2 antibody to a patient who's cancer does not overexpress ErbB2, particularly in light of the lack of predictable function of ErbB2 antibodies set forth above, the unpredictability of cancer treatments set forth above, and the lack of guidance regarding the mechanism of action of the antibody.

Thus the disclosure of one antibody which binds ErbB2 and blocks binding of one ErbB receptor to a single ligand is insufficient support under the first paragraph of 35 U.S.C 112 for claims which encompass any and all antibodies which bind ErbB2 and block binding by any ErbB ligand, including the specific interactions recited in the claims, and those yet undiscovered. The courts have held that:

"Inventor should be allowed to dominate future patentable inventions of others where those inventions were based In some way on his teachings, since some improvements while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; however, he must not be permitted to achieve this dominance by claims which are insufficiently supported and hence, not In compliance with the first paragraph of U.S.C. 112; that paragraph requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill In the art; In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement In the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific law; In cases involving

unpredictable factors, such as chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved."In re Fisher 427 F.2d 833, 166 USPQ 18 (CCPA 1970).

In the instant case, the degree of unpredictability of both antibody activity and treatment efficacy is high, as set forth above.

Further, with regard to claims 8 and 27, drawn to administration of an antibody which treats cancer which does not overexpress ErbB2, as set forth above, while it is reasonable to determine that administration of an anti- ErbB2 antibody might inhibit EGFR/ ErbB2 interactions, it is not clear how this might work if a cell does not express ErbB2. There is no guidance or objective evidence that an antibody which binds ErbB2 would have any effect at all on a cell which does not express the ErbB2 receptor. Although Example 7 of the instant application sets forth an in vitro assay in which a cell line which expresses but does not "overexpress" ErbB2 exhibits a reduction in tumor growth after administration of 2C4, there is no control antibody or cell line in this sample, and so the specific effect of the anti-ErbB2 antibody 2C4 cannot be determined. Further, the example tests a single cell line, in vitro, which is administered a single species of ErbB2 antibody and thus it is not clear that results obtained from this assay would correlate to generalized results of administering an anti ErbB2 antibody to a patient who's cancer does not overexpress ErbB2, particularly in light of the lack of predictable function of ErbB2 antibodies set forth above, the unpredictability of cancer treatments set forth above, and the lack of guidance regarding the mechanism of action of the antibody.

Therefore it would require undue experimentation to practice the invention commensurate in scope with the claims.

10. Claims 3 and 16-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not set forth in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification lacks complete deposit information for the deposit of the antibody 2C4. While the specification provides enough information for one of skill in the art to produce an antibody with the same or similar properties as 2C4, reproduction of an identical 2C4 is an unpredictable event. Because it does not appear that 2C4 is publicly available or can be reproducibly isolated from nature without undue experimentation and because certain of the claims specially require the use of 2C4, a suitable deposit of 2C4 for patent purposes is required or evidence must be provided that 2C4 is well known and readily available to the public.

Furthermore, unless the deposit was made at or before the time of filing, a declaration filed under the 37 C.F.R. 1/132 is necessary to construct a chain of custody. The declaration, executed by a person in a position to know, should identify the deposited antibody by its depository accession number, establish that the deposited antibody is the same as that described in the specification, and establish that the deposited antibody was in applicant's possession at the time of filing. See In re Lundak, 773 F.2d. 1216, 227 U.S.P.?Q. 90 (Fed. Cir. 1985).

It is not clear from the disclosure that deposits of 2C4 meet all the criteria set forth in MPEP 608/01 (p)(C), items 1-3. Assurance of compliance may be in the form of a declaration or averment under oath. A suggested format for such a declaration or averment is outlined below:

SUGGESTION FOR DEPOSIT OF BIOLOGICAL MATERIAL

A declaration by applicant, assignee, or applicant's agent identifying a deposit of biological material and averring the following may be sufficient to overcome an objection and rejection based on a lack of availability of biological material.

1. Identifies declarant.
2. States that a deposit of the material has been made in a depository affording permanence of the deposit and ready accessibility thereto by the public if a patent is granted. The depository is to be identified by name and address.
3. States that the deposited material has been accorded a specific (recited) accession number.
4. States that all restrictions on the availability to the public of the material will be irrevocably removed upon the granting of a patent.
5. States that the material has been deposited under conditions that ensure that access to the material will be available during the pendency of the patent application to one determined by the Commissioner to be entitled thereto under 35 CFR 1.14 and 35 USC 122.
6. States that the deposited material will be stored with all care necessary to keep it viable and uncontaminated for a period of at least five years after the most recent request for the furnishing of a sample of the deposited microorganism, and in any case at least thirty (30) years after the date of a deposit or for the enforceable life of the patent, whichever is longer.
7. Acknowledges the duty to replace the deposit should the depository be unable to furnish a sample when requested due to the condition of the deposit.
8. That he/she declares further that all statements made therein of his/her own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issuing thereon.

Additionally, the deposit must be referred to in the body of the specification and be identified by deposit (accession) number, name and address of the depository, and the complete taxonomic description.

As a possible means of completing the record, applicants may submit a copy of the deposit receipt.

11. Prior to setting forth the following art rejections, it is noted that the claims are interpreted to encompass cancers which express EGFR and concurrently overexpress ErbB2. It is known in the art that EGFR (ErbB1) and ErbB2 are often co-expressed in cancer, and further often interact with each other in a common tyrosine kinase activation pathway. See Jardines et al., Pathobiology, Vol. 61, pages 268-282, 1993, page 278, column 2, which determines that many ErbB2 positive patients also overexpress EGFR. Further, Earp et al. teaches that EGFR is overexpressed in "virtually every epithelial malignancy". Additionally it is noted that HER2 and EGFR can interact in an EGF/TGF-alpha dependent manner. (see page 121).

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2)

voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

13. Claims 1-2, 4-6, 12, and 20 are rejected under 35 U.S.C. 102(e) as being anticipated by Greene et al., US Patent 5,824,311, published October 20, 1998 (IDS # 8), as evidenced by Jardines et al., Pathobiology, Vol. 61, pages 268-282, 1993, or Earp et al., Breast Cancer Research and Treatment, Vol. 35, pages 115-132, 1995 (IDS # 38).

Greene et al., US Patent 5,824,311 teaches a method of treating a patient, which includes humans, by administering a therapeutically effective amount of an antibody which binds ErbB2 and blocks ligand activation of an ErbB receptor. Specifically, Greene teaches that the p185 oncogene (which is the same as ErbB2) has been found active in lung adenocarcinoma, and further provides a method of using monoclonal antibodies which bind to ErbB2 to treat mammalian cancer tumors which express a translation of the neu oncogene on their surfaces (see column 3, line 50-column 5). The antibody of Greene et al. is not conjugated to a cytotoxic compound.

While Greene et al. does not explicitly recite that the cancer which is treated expresses or overexpresses EGFR, or overexpresses an ErbB ligand, including TGF-alpha, numerous cancers which express ErbB2 inherently co-express, or concurrently overexpress EGFR, and/or the ErbB ligand TGF-alpha. See Jardines et al., Pathobiology, Vol. 61, pages 268-282, 1993, page 278, column 2, which determines

that many ErbB2 positive patients also overexpress EGFR and that the ErbB ligand TGF-alpha is expressed at higher levels in malignancies. Further, Earp et al. teaches that EGFR is overexpressed in "virtually every epithelial malignancy", and that TGF-alpha and other EFG family members are overexpressed in cancer. Additionally it is noted that HER2 and EGFR can interact in an EGF/TGF-alpha dependent manner. (see page 121).

14. Claims 1-2, 4-6, and 20 are rejected under 35 U.S.C. 102(e) as being anticipated by Arakawa et al., US Patent 5,783,186 (IDS #6), published July 21, 1998, or Hudziak et al., US Patent 5,725,856, published March 10, 1998, as evidenced by Jardines et al., Pathobiology, Vol. 61, pages 268-282, 1993, or Earp et al., Breast Cancer Research and Treatment, Vol. 35, pages 115-132, 1995 (IDS #38).

Arakawa et al., US Patent 5,783,186 teaches a method of treating a patient, which includes humans, ~~by administering~~ by administering a therapeutically effective amount of an antibody which binds ErbB2 and blocks activation of an ErbB receptor. Specifically, Arakawa teaches that the HER2 oncogene (which is the same as ErbB2) has been found active in numerous cancers, including breast, ovarian, gastric, prostate, and colorectal, and further provides a method of using monoclonal antibodies which bind to ErbB2 to treat mammalian cancer tumors which express ErbB2 on their surfaces (see column 6, lines 12-17, and lines 53-59). The antibody of Arakawa et al. is not conjugated to a cytotoxic compound.

Hudziak et al., US Patent 5,725,856 teaches a method of treating a patient, which includes humans, by administering a therapeutically effective amount of an antibody which binds ErbB2 and blocks activation of an ErbB receptor. Specifically, Hudziak teaches that the HER2 oncogene (which is the same as ErbB2) has been found active in numerous cancers, including breast, renal, gastric and salivary cancers, and further provides a method of using monoclonal antibodies which bind to ErbB2 to treat mammalian cancer tumors which express ErbB2 on their surfaces (see column 4, lines 27-31, column 6, lines 31-35, column 7, lines 50-56, column 8, lines 27-30, column 10, lines 46-53, column 11, lines 32-40). The antibody of Hudziak et al. is not conjugated to a cytotoxic compound. Hudziak et al. also teaches that EGFR and TGF-alpha are associated with an increased proliferative effect in a carcinoma cell line (column 3, lines 28-65)

While Arakawa et al. and Hudziak et al. do not explicitly recite that the cancer which is treated expresses or overexpresses EGFR, or overexpresses an ErbB ligand, including TGF-alpha, numerous cancers which express ErbB2 inherently co-express, or concurrently overexpress EGFR, and/or the ErbB ligand TGF-alpha. See Jardines et al., page 278, which determines that many ErbB2 positive patients also overexpress EGFR and that the ErbB ligand TGF-alpha is expressed at higher levels in malignancies. Further, Earp et al. teaches that EGFR is overexpressed in "virtually every epithelial malignancy", and that TGF-alpha and other EFG family members are overexpressed in cancer. Additionally it is noted that HER2 and EGFR can interact in an EGF/TGF-alpha dependent manner. (see page 121).

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claims 1-2, 4-6, 12-13, 18, 20-21, and 24-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grim et al., Am. J. Respir. Cell Mol. Biol., Vol. 15, pages 348-354, September 1996, or Kern et al., Am. J. Respir. Cell Mol. Biol., Vol. 9, pages 448-454, 1993, as evidenced by Jardines et al., Pathobiology, Vol. 61, pages 268-282, 1993, or Earp et al., Breast Cancer Research and Treatment, Vol. 35, pages 115-132, 1995 (IDS #38), in view of Baselga et al., Oncology, Suppl. 2, March 1997, pages 43-48 (Baselga I), or Baselga et al., Journal of Clinical Oncology, Vol. 14, No. 3, pages 737-744, March 1996 (Baselga II) (IDS #24).

Grim et al. teaches a method of treating lung cancer by administering an antibody fragment which binds to ErbB2 (see abstract, and especially pages 350 and 353).

Kern et al. teaches a method of treating non-small cell lung cancer by administering an antibody (4D5) which binds to ErbB2 (see abstract, and pages 449-450, and 452-453).

While Grim et al. and Kern et al. do not explicitly recite that the cancer which is treated expresses or overexpresses EGFR, or overexpresses an ErbB ligand, including TGF-alpha, numerous cancers which express ErbB2 inherently co-express, or concurrently overexpress EGFR, and/or the ErbB ligand TGF-alpha. See Jardines et al., page 278, which determines that many ErbB2 positive patients also overexpress EGFR and that the ErbB ligand TGF-alpha is expressed at higher levels in malignancies. Further, Earp et al. teaches that EGFR is overexpressed in "virtually every epithelial malignancy", and that TGF-alpha and other EFG family members are overexpressed in cancer. Additionally it is noted that HER2 and EGFR can interact in an EGF/TGF-alpha dependent manner. (see page 121).

Grim et al., and Kern et al. fail to teach treatment of human cancer patients.

Baselga I teaches a method of treatment of a human patient diagnosed with a disorder characterized by over expression of ErbB2 receptor comprising administering an effective amount of an anti-ErbB2 antibody which binds the ErbB2 extracellular domain, and further discusses dosage determinations, including weekly dosages and dosages which are between 0.5mg/kg and 10 mg/kg (page 46).

Baselga II teaches a method of treatment of a human patient diagnosed with a disorder characterized by over expression of ErbB2 receptor comprising administering an effective amount of an anti-ErbB2 antibody which binds the ErbB2 extracellular domain (see for example, abstract).

Therefore it would be *prima facie* obvious to one of ordinary skill in the art at the time of applicant's invention to use the method of treating lung cancer cells to

treat humans having lung cancer, and one would have been motivated to do so because anti-ErbB2 antibodies function in vitro to treat lung cancer cells, as taught by Grim et al. and Kern et al., and further are an effective treatment for humans having a ErbB2 positive cancer, as taught by Baselga I and Baselga II. It also would have been *prima facie* obvious to use doses from about 0.5 mg/kg to about 10 mg/kg, administered weekly or every three weeks in the method because optimization of the dosage of the composition to provide an optimal response is well within the ordinary skill in the art of cancer therapy, as evidenced by Baselga I, which discusses dosage determinations, including weekly dosages and dosages which are between 0.5mg/kg and 10 mg/kg

17. Claims 1-2, 4-6, 12-13, 18, and 20-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arakawa et al., US Patent 5,783,186, published July 21, 1998 (IDS #6), or Hudziak et al., US Patent 5,725,856, published March 10, 1998, as evidenced by Jardines et al., Pathobiology, Vol. 61, pages 268-282, 1993, or Earp et al., Breast Cancer Research and Treatment, Vol. 35, pages 115-132, 1995 (IDS #38), in view of Grim et al., Am. J. Respir. Cell Mol. Biol., Vol. 15, pages 348-354, September 1996, or Kern et al., Am. J. Respir. Cell Mol. Biol., Vol. 9, pages 448-454, 1993.

Arakawa et al. and Hudziak et al., teach as applied to claims 1-2, 4-6, and 20 supra.

Hudziak et al., and Arakawa et al. fail to teach that the anti-ErbB2 antibody can be used to treat lung cancer and non-small cell lung cancer.

Grim et al. teaches a method of treating lung cancer by administering an antibody fragment which binds to ErbB2 (see abstract, and especially pages 350 and 353).

Kern et al. teaches a method of treating non-small cell lung cancer by administering an antibody (4D5) which binds to ErbB2 (see abstract, and pages 449-450, and 452-453).

Therefore it would be *prima facie* obvious to one of ordinary skill in the art at the time of applicant's invention to treat human lung cancer patients with an ErbB2 antibody, and one would have been motivated to do so because anti-ErbB2 antibodies function in vitro to treat lung cancer cells, as taught by Grim et al. and Kern et al., and further are an effective treatment for humans having a ErbB2 positive cancer, as taught by Hudziak et al., and Arakawa et al.

18. Claims 1-7, 12-13, 16-18, 20-21, and 24-26 are rejected under 35 U.S.C. 103(a) as being anticipated by Greene et al., US Patent 5,842,311, published October 20, 1998 (IDS # 8), or Arakawa et al., US Patent 5,783,186, published July 21, 1998 (IDS #6), or Hudziak et al., US Patent 5,725,856, published March 10, 1998, as evidenced by Jardines et al., Pathobiology, Vol. 61, pages 268-282, 1993, or Earp et al., Breast Cancer Research and Treatment, Vol. 35, pages 115-132, 1995 (IDS #38), and Grim et al., Am. J. Respir. Cell Mol. Biol., Vol. 15, pages 348-354, September 1996, or Kern et al., Am. J. Respir. Cell Mol. Biol., Vol. 9, pages 448-454, 1993, and Baselga et al., Oncology, Suppl. 2, March 1997 (Baselga I), or Baselga et al., Journal of Clinical

Oncology, Vol. 14, No. 3, pages 737-744, March 1996 (Baselga II), in view of Fendly et al., Cancer Research, Vol. 50, pages 1550-1558, March 1, 1990 (IDS #39), or Shepard et al., Journal of Clinical Immunology, Vol. 11, No. 9, pages 117-126, 1991 (IDS #93).

Greene et al., Arakawa et al., Hudziak et al., Jardines et al., Earp et al., Grim et al., Kern et al., (Baselga I), or (Baselga II), teach as applied to claims 1-2, 4-6, 12-13, 18, 20-21, and 24-26 supra.

Greene et al., Arakawa et al., Hudziak et al., Jardines et al., Earp et al., Grim et al., Kern et al., (Baselga I), or (Baselga II), fail to teach an antibody which blocks binding of 2C4 or the specific monoclonal antibody 2C4, or an antibody which blocks TGF-alpha activation of MAPK.

Fendly et al. teaches the monoclonal antibody 2C4, and that the antibody selectively binds ErbB2 (see for example, page 1552). While Fendly et al. does not explicitly recite that 2C4 blocks TGF-alpha activation of MAPK, this would be an inherent characteristic of the antibody.

Shepard et al. teaches the monoclonal antibody 2C4, and that the antibody selectively binds ErbB2 and is capable of treating ErbB2 positive cells line (see for example, page 123). While Shepard et al. does not explicitly recite that 2C4 blocks TGF-alpha activation of MAPK, this would be an inherent characteristic of the antibody.

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the 2C4 antibodies of Fendly et al. and Shepard et al., in the methods of Greene et al., Arakawa et al., Hudziak et al.,

Jardines et al., Earp et al., Grim et al., Kern et al., (Baselga I), or (Baselga II), and one would have been motivated to do so because these antibodies selectively bind to ErbB2 and are able to treat cells which overexpress ErbB2, as taught by Fendly et al., and Shepard et al.

19. Claims 1-7, 12-13, 16-21, and 24-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Greene et al., US Patent 5,842,311, published October 20, 1998 (IDS #8), or Arakawa et al., US Patent 5,783,186, published July 21, 1998 (IDS #6), or Hudziak et al., US Patent 5,725,856, published March 10, 1998, as evidenced by Jardines et al., Pathobiology, Vol. 61, pages 268-282, 1993, or Earp et al., Breast Cancer Research and Treatment, Vol. 35, pages 115-132, 1995 (IDS #38), and Grim et al., Am. J. Respir. Cell Mol. Biol., Vol. 15, pages 348-354, September 1996, or Kern et al., Am. J. Respir. Cell Mol. Biol., Vol. 9, pages 448-454, 1993, and Baselga et al., Oncology, Suppl. 2, March 1997 (Baselga I), or Baselga et al., Journal of Clinical Oncology, Vol. 14, No. 3, pages 737-744, March 1996 (Baselga II) (IDS #24), in view of Fendly et al., Cancer Research, Vol. 50, pages 1550-1558, March 1, 1990 (IDS #39), or Shepard et al., Journal of Clinical Immunology, Vol. 11, No. 9, pages 117-126, 1991 (IDS #93), all in view of Schlom, Molecular Foundations of Oncology, pages 95-134, 1991.

Greene et al., Arakawa et al., Hudziak et al., Jardines et al., Earp et al., Grim et al., Kern et al., (Baselga I), (Baselga II), Fendly et al., or Shepard et al., teach as applied to claims 1-7, 12-13, 16-18, and 20-21 supra.

Greene et al., Arakawa et al., Hudziak et al., Jardines et al., Earp et al., Grim et al., Kern et al., (Baselga I), (Baselga II), Fendly et al., or Shepard et al., fail to teach antibody fragments, including Fab's, and the specific dosages recited claims 24-25.

Schlom described the various known antibody modifications, including Fab's and that they provide the therapeutic advantage of reducing the host anti-Mab response (see pages 112-123).

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the Fab's of Schlom in the methods of Greene et al., Arakawa et al., Hudziak et al., Jardines et al., Earp et al., Grim et al., Kern et al., (Baselga I), (Baselga II), Fendly et al., or Shepard et al., and one would have been motivated to do so because they reduce the host anti-Mab response.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E Hunt whose telephone number is (703) 308-7548. The examiner can normally be reached on Monday-Friday, 6-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703)308-0196.

Jennifer E Hunt
Examiner
Art Unit 1642

jeh
February 25, 2002

SHEELA HUFF
PRIMARY EXAMINER